REMARKS

Claims 1, 2, 4, 7, 8 and 10-15 are pending.

Claims 2 and 14 have been canceled herein, and new claims 16-19 have been added.

Applicants acknowledge the Examiner's new grounds of rejection of claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶1 for alleged new matter relating to the recitation of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO:36." Applicants respectfully traverse this rejection.

Applicants acknowledge that the Examiner has maintained rejections of claims 1,2, 4, 7, 8 and 13-15, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description for "contiguous CpG islands of SEQ ID NO:34-37. Applicants have amended claims 7 and 8, but respectfully traverse this rejection with respect to the other claims.

Applicants additionally acknowledge that the Examiner has maintained rejections of claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement. Applicants have amended claims 7 and 10, but respectfully traverse this rejection with respect to the other claims.

Applicants further acknowledge that the Examiner has rejected claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶2 based on alleged indefiniteness with respect to recitation of "coordinately hypermethylated." Applicants respectfully traverse this rejection, based on the teachings of the originally filed specification.

No new matter has been added.

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Alleged New Matter

The Examiner has rejected claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶1 for alleged new matter relating to applicants' recitation of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO:36."

Specifically, the Examiner asserts that the concept of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO:36" does not appear to be part of the originally filed invention (Office action of 14 February 2005 at page 3).

Applicants respectfully traverse this rejection. Specifically, the specification at page 7, ll. 19-23 teaches (in reference to Tables I & II) that 55 out of the 103 nucleic acid sequences (including SEQ ID NOS:36 and 37) correspond to CpG islands. Additionally, the specification at page 8, ll. 12-22 teaches that the "methylation state of a portion of a CpG island is generally representative of the island as a whole," and that the present invention therefore further encompasses the CpG islands contiguously associated with the 55 sequences. Therefore, the specification teaches that larger CpG islands are comprised of CpG island portions, and that the methylation state of a CpG dinucleotide in, for example, SEQ ID NO:36 (a CpG within a "portion") is representative of that of a larger contiguous CpG island (a CpG of the "whole"), and therefore that for a given DNA sample, the CpG dinucleotide state within the portion is *coordinate* with the CpG dinucleotide methylation state of the whole.

Applicants have cancelled claims 2 and 14 in view of new claims 16 and 18.

Applicants, therefore, respectfully request withdrawal of this rejection, based on the fact that the originally filed specification and claims teach coordinate methylation states between CpGs of a larger CpG island and CpGs of a portion thereof.

Rejections under 35 U.S.C. § 112, ¶1

Written description:

The Examiner has maintained the rejection of claims 1,2, 4, 7, 8 and 13-15, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description for "contiguous CpG islands of SEQ ID NO:34-37. Applicants have amended claims 7 and 8, but respectfully traverse this rejection with respect to the other claims.

Specifically the Examiner asserts that the "specification fails to describe contiguous CpG islands of SEQ ID NOS:34-37," and further that "no precise definition, such as by structure,

formula, chemical name, or physical properties has been provided" (Office action of 14 February 2005 at page 5).

Applicants respectfully their traverse of this rejection, based on the fact that applicants have in fact provided a *formula*, *physical properties* and *structure* sufficient to describe contiguous CpG islands of SEQ ID NOS:34-37. Specifically, the specification at page 5 and 8 teaches a formula; namely, "a CpG island sequence associated with a particular SEQ ID NO sequence of the present invention is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6), and a GC Content >0.5. Physical properties and structure are also implicit within this definition, because the definition absolutely requires that the associated sequence is contiguous with the portion of the CpG island. Applicants contend, therefore, that the relevant sequences are sufficiently described because of the formula and requirement for physical linkage along the chromosome, because a person of ordinary skill in the art would be able to determine, without undue experimentation what these sequences are, based on applicant originally filed disclosure. In this sense, all relevant DNA sequences are described, and sufficiently available to enable those of ordinary skill to practice the invention as claimed.

With respect to claims 7 and 8, applicants have responsively amended independent claim 7 to recite "consisting of at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOS:36 and 37, and the bisulfite-converted sequences thereof," and further recites, in (b) "wherein the kit, based at least in part on the probe or primer, is suitable to determine the methylation status of one or more CpG dinucleotides within the sequence selected from the group consisting of SEQ ID NOS:36 and 37."

Independent claim 10 has been amended to recite "*consisting* of a methylated or unmethylated polynucleotide sequence selected from the group consisting of sequences of SEQ ID NO:37, and the bisulfite-converted sequences thereof."

Support for these amendments is, for example, inherent to the originally filed claims.

Applicants have cancelled claim 2 in view of new claim 16.

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1,2, 4, 7, 8 and 13-15, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description.

Further Rejections under 35 U.S.C. § 112, ¶1

Enablement:

The Examiner has maintained rejections of claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement.

Specifically, the Examiner asserts: (**1**) that the claims, in addition to SEQ ID NOS:36 and 37, also encompass SEQ ID NOS:34, 35 and 38, and that with respect to SEQ ID NOS:34, 35 and 38 it is unpredictable whether hypermethylation is a marker for cancer, and that the artisan would be required to sample a population of individuals and assess, by undue unpredictable trial and error, whether each of these sequences is associated or differentially expressed in cancer (Office action of 14 February 2005 at pages 8-10); and (**2**) citing Toyota et al., that the specification has not taught that a predictable correlation exists between SEQ ID NOS:36 and 37, and coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 or 37, and that it is therefore unpredictable whether coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 or 37 are indicative of cancers absent undue experimentation " (Office action of 14 February 2005 at page 10-11).

With respect to (**1**) above, applicants have responsively amended claims 7 and 10 to delete recitation of SEQ ID NOS:34, 35 and 38.

Applicants maintain their traversal, with respect to (**2**) above and contend that recitation of coordinately methylated contiguous CpG islands encompasses (and despite Toyota cited by the Examiner) only those contiguous CpG island dinucleotide sequences that would correlate (along with those of SEQ ID NOS:36 and 37) with the respective cancer(s). Furthermore, applicants maintain their contention that it would not entail undue experimentation to determine whether a CpG dinucleotide of a contiguous CpG island that comprises SEQ ID NO:36 or 37 is coordinately methylated with a CpG of SEQ ID NO:36 or 37. Such a CpG island is readily identifiable and analyzable because it is structurally defined as being contiguous to applicant's disclosed sequence and is further defined and describe by applicant's formula describe herein above. Isolation of such

a CpG island sequence from a cancer tissue and determining the methylation state of one or more CpG residues therein relative to a control, could be done by one of ordinary skill in the art in a matter of a few days or a week using standard DNA manipulation methods and methylation assays available at the time of filing of the present application. This does not represent undue experimentation as asserted by the Examiner.

Applicants, in view of the above-described amendments and comments, respectfully request withdrawal of the Examiner's enablement rejection of amended claims 1, 4, 7, 8 and 10-13 and 15. Claims 2 and 14 have been cancelled herein. No new matter has been added.

Rejection under 35 U.S.C. § 112 ¶2

The Examiner has rejected claims 1, 2, 4, 7, 8 and 10-15 under 35 U.S.C. § 112 ¶2, based on alleged indefiniteness with respect to recitation of "coordinately hypermethylated."

Specifically, the Examiner asserts that it is unclear what is meant by "coordinately hypermethylated" (*e.g.*, whether is refers to the amount or location) and how this definition is related to hypermethylation (Office action of 14 February 2005 at page 15).

Applicants respectfully traverse this rejection, based on the teachings of the originally filed specification.

Specifically, as described above, the specification at page 7, ll. 19-23 teaches (in reference to Tables I & II) that 55 out of the 103 nucleic acid sequences (including SEQ ID NOS:36 and 37) correspond to CpG islands. Additionally, the specification at page 8, ll. 12-22 teaches that the "methylation state of a portion of a CpG island is generally representative of the island as a whole," and that the present invention therefore further encompasses the CpG islands contiguously associated with the 55 sequences. Therefore, the specification teaches that larger CpG islands are comprised of CpG island portions, and that the methylation state of a CpG dinucleotide in, for example, SEQ ID NO:36 (a CpG within a "portion") is representative of that of a larger contiguous CpG island (a CpG of the "whole"), and therefore that for a given DNA sample, the CpG dinucleotide state within the portion is *coordinate* with the CpG dinucleotide methylation

state of the whole.

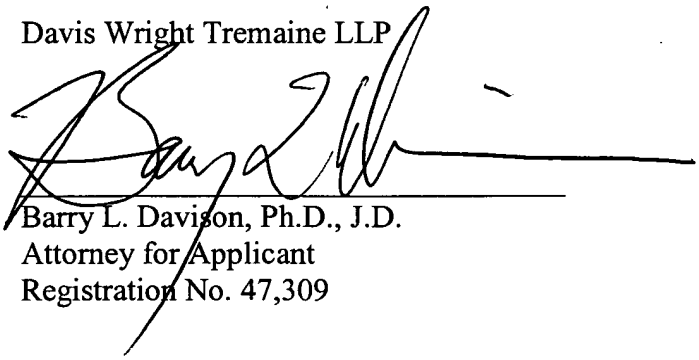
Therefore, recitation of coordinate methylation refers to the methylation state of any CpG in a larger CpG island that is concordant with the methylation state of a CpG in a portion thereof. Applicants have amended independent claims 1 and 13 to recite "coordinately methylated" instead of "coordinately hypermethylated," because recitation of hypermethyation is already present in step c) of these claims.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration of the claimed invention, entry of the present responsive Amendment and allowance of all pending claims, including new claims 16-19..

Respectfully submitted,

Davis Wright Tremaine LLP



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